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(21) International Application Number: PCT/EP91/01137 (22) International Filing Date: 19 June 1991 (19.06.91) (30) Priority data: 540,980 20 June 1990 (20.06.90) US (71) Applicant: SCHERING AKTIENGESELLSCHAFT, BERLIN UND BERGKAMEN [DE/DE]; Müllers- trasse 170-178, D-1000 Berlin 65 (DE). (72) Inventors: CHOU, You-Ling ; 73 Michel Avenue, Piscata- way, NJ 08854 (US). ERHARDT, Paul, William ; 12 Ap- gar Road, Long Valley, NJ 07853 (US). HAGEDORN, Alfred, Arthur ; 57 Eardley Road, Edison, NJ 08817 (US). LAMPE, John, W. ; 18 Algonquin Avenue, Rocka- way, NJ 07866 (US). LUMMA, William, Carl, Jr. ; 25 Newman Road-M.R.L., Pennsburg, PA 18073 (US). MORGAN, Thomas, Kenneth ; 47 Sherman Avenue, Morris Plains, NJ 07950 (US). WIGGINS, Jay, Ross ; R.R. 1, Box 2701, Hamburg, NJ 07419 (US).		(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (Eu- ropean patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European pa- tent), NL (European patent), SE (European patent). Published <i>With international search report.</i>
(54) Title: IMIDAZOLYLBENZOYL SUBSTITUTED HETEROCYCLES (57) Abstract Novel imidazolylbenzoyl substituted heterocycles and their use as cardiovascular agents most especially as Class III an- tiarrhythmic agents is described. Pharmaceutical formulations containing such compounds are also discussed.		

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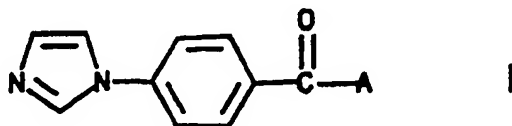
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IMIDAZOLYL BENZOYL SUBSTITUTED HETEROCYCLES

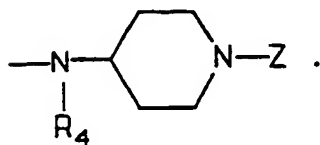
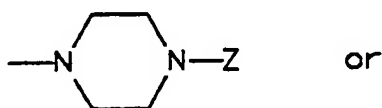
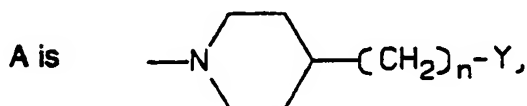
GENERAL DESCRIPTION OF THE INVENTION

Composition-of-Matter Aspect

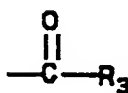
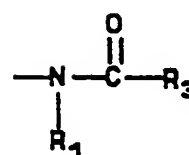
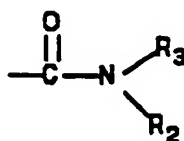
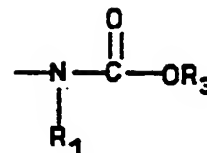
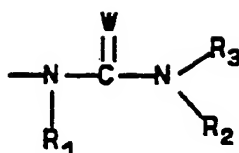
In its composition-of-matter aspect this invention relates to novel imidazolylbenzoyl substituted heterocycles and their pharmaceutically acceptable salts. Particularly, this invention relates to novel compounds defined by the following Formula I:



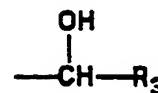
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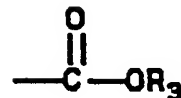
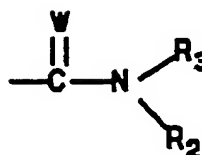
Y is selected from



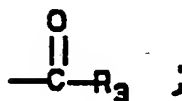
or



Z is selected from



or



W is selected from O, S, NR, NCN or CHNO₂.

R is selected from hydrogen, C₁-C₄ straight or branched chain alkyl, optionally substituted aryl or arylalkyl.

R_1 , R_2 , R_4 are independently hydrogen or C_1 - C_4 straight or branched chain alkyl.

R_3 is selected from C_1 - C_8 straight or branched chain alkyl, optionally substituted aryl or arylalkyl, or heteroaryl;

n is selected from the integers 0, 1 or 2,
and the pharmaceutically acceptable salts thereof.

Provisos in the foregoing Formula I and definition thereof are that when R_3 is a C_1 - C_8 straight or branched chain alkyl this is not inclusive of a tertiary moiety and when R_3 is heteroaryl, said heteroaryl cannot be attached to a hetero atom eg. N or O.

Also contemplated as part of this invention are the pharmaceutically acceptable salts of the compounds of Formula I. Useful acids for this purpose include inorganic acids such as hydrobromic, hydrochloric, sulfuric, phosphoric and organic acids such as acetic, propanoic, benzoic, naphthalenecarboxylic, oxalic, succinic, malic, adipic, lactic, tartaric, citric, salicylic, methanesulfonic and p-toluenesulfonic.

It is to be understood that the definition of the compounds of Formula I encompasses all possible stereoisomers and mixtures thereof, which

possess the activity discussed below. In particular, it encompasses racemic modifications and any optical isomers which possess the indicated activity.

It is also to be understood that the definition of the compounds of Formula I encompasses all possible polymorphic modifications and other solid state modifications which possess the stated activity.

In the foregoing Formula I, various terms are defined in the following manner. The term C₁-C₄ straight or branched chain alkyl shall refer to, for example, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tertiary butyl and sec-butyl. The term C₁-C₈ straight or branched chain alkyl shall be inclusive of but not limited to such moieties as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, pentyl, neo-pentyl, hexyl, 3-methylpentyl, heptyl, 2-methylhexyl, octyl, 2-ethylhexyl but will not include the tertiary alkyl moiety. The term aryl shall refer to a phenyl group, and the term arylalkyl shall refer to a phenyl at the terminus of a C₁-C₄ straight carbon chain. The term optionally substituted shall refer to substitution on the phenyl ring and shall be of 1 to 3 in number and selected from C₁-C₄ straight chain alkoxy, chlorine, fluorine or bromine. The substitution on the phenyl ring may also be a mono 1-imidazolyl. The term heteroaryl is defined as a pyridyl optionally substituted by C₁-C₄ straight chain alkyl, thiophenyl or furyl.

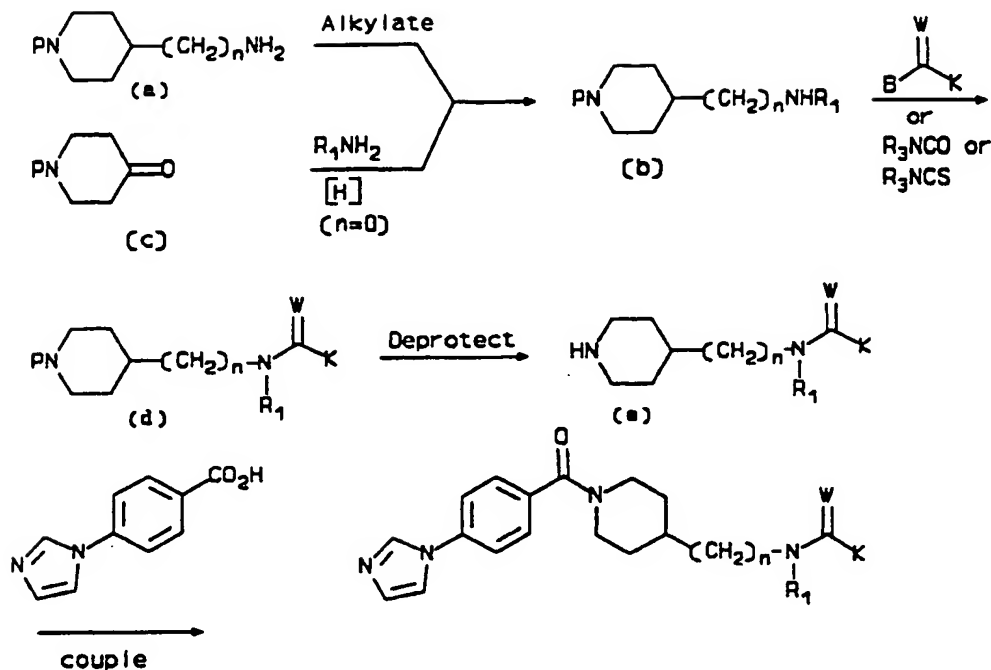
The compounds which follow are some of those which serve to exemplify various aspects of the invention described herein.

- a. N-[2-(4-Chlorophenyl)ethyl]-N'-[2-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidiny]ethyl]-N'-methylthiourea.
- b. N,N-Diethyl-N'-[[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidiny]methyl]guanidine.
- c. N"-Cyano-N-ethyl-N'-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidiny]-N-[[4-(1H-imidazol-1-yl)phenyl]methyl]guanidine.
- d. 2-Butylamino-2-[[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidiny]amino]-1-nitroethene.
- e. N-[3-(3,4-Dimethoxyphenyl)propyl]-N'-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidiny]urea.
- f. N-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidiny]-N'-(4-methylpentyl)urea.
- g. N-Butyl-4-[4-(1H-imidazol-1-yl)benzoyl]-N-methylpiperazine-1-carbothioamide.
- h. N-(3-Chlorophenyl)-4-[4-(1H-imidazol-1-yl)benzoyl]-N'-methyl-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine-1-carboximidamide.

- i. N-Butyl-N'-cyano-N-ethyl-4-[4-(1H-imidazol-1-yl)benzoyl]-piperazine-1-carboximidamide.
- j. 4-[4-(1H-imidazol-1-yl)benzoyl]piperazine-1-carboxylic acid butyl ester.
- k. 1-[(5-Methyl-2-pyridinyl)carbonyl]-4-[4-(1H-imidazol-1-yl)-benzoyl]piperazine.
- l. N-[1-(1-Dipropylamino-2-nitroethenyl)-4-piperidinyl]-4-(1H-imidazol-1-yl)-N-methylbenzamide.
- m. 4-[[4-(1H-imidazol-1-yl)benzoyl](methyl)amino]-N,N,N'-tripropylpiperidine-1-carboximidamide.
- n. N-[2-(4-Chlorophenyl)ethyl]-N'-cyano-4-[[4-(1H-imidazol-1-yl)-benzoyl]amino]-N-methylpiperidine-1-carboximidamide.
- o. 4-(1H-imidazol-1-yl)-N-[1-(2-thienylcarbonyl)-4-piperidinyl]-benzamide.

Process Aspect

In general the compounds of Formula I may be prepared as shown in Schemes A-F.

SCHEME A

In Scheme A, P is a temporary protecting group for nitrogen such as benzyl, benzyloxycarbonyl, *t*-butoxycarbonyl, benzoyl, or acetyl; R_1 and R_2 are lower alkyl or hydrogen, R_3 is $\text{C}_1\text{--C}_8$ straight or branched chain alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl or heteroaryl, with the proviso that R_3 is not tertiary alkyl; R_4 is loweralkyl or hydrogen; W is oxygen, sulfur, NR, NCN, or CHNO_2 ; K is R_3 , OR_3 , or NR_2R_3 ; B is a suitable leaving group such as chlorine, bromine, thiomethyl, thiophenyl, phenoxy, 1-imidazolyl and $n=0\text{--}2$.

The aminoalkylpiperidines (b) are conveniently prepared by alkylation of the primary amines (a). Typically, the amine (a) is treated with 1 to 2

The aminoalkylpiperidines (b) are conveniently prepared by alkylation of the primary amines (a). Typically, the amine (a) is treated with 1 to 2 equivalents of aldehyde or ketone in an organic solvent, most generally methanol, in the presence of molecular sieves. In some cases, it proves advantageous to add acid to the reaction mixture to maintain a slightly acidic pH. A reducing agent, most commonly sodium cyanoborohydride, is added to the mixture, and the reaction is stirred from 1 to 48 hr at temperatures from 0°C to 40°C. The alkylated product (b) may be isolated by standard methods; for example, partitioning between organic and aqueous phases, standard chromatographic purification, and crystallization.

In some cases when $n=0$, it is preferable to prepare compounds (b) by reductive amination of the corresponding piperidones (c). The reductive amination is carried out in a fashion similar to that described above. Thus, the piperidone (c) and 0.5 to 1 equivalents of a primary amine are combined in an organic solvent such as methanol in the presence of molecular sieves, and optionally in the presence of added acid. A reducing agent such as sodium cyanoborohydride is added, and the reaction mixture is stirred from 1 to 48 hr at 0°C to 40°C, after which standard procedures are used to isolate the product (b).

Reactions of amines (b) to give derivatized amines (d) follow methods appropriate to the specific derivatizing agent. In general, the amine (b) is treated with from 1 to 2 equivalents of the derivatizing reagent in an inert

organic solvent, such as methylene chloride, acetonitrile, pyridine, or dimethylformamide, at temperatures from 0°C to 100°C, for periods of from 0.5 to 48 hr. Some cases may be carried out advantageously in a two-phase mixture of an organic solvent and an aqueous solution of an inorganic base. The addition of 1 to 3 equivalents of a tertiary amine base is beneficial in some cases, as is the use of an inert atmosphere such as nitrogen. Products (d) are isolated by extractive workup, and are purified by standard crystallization or chromatographic methods.

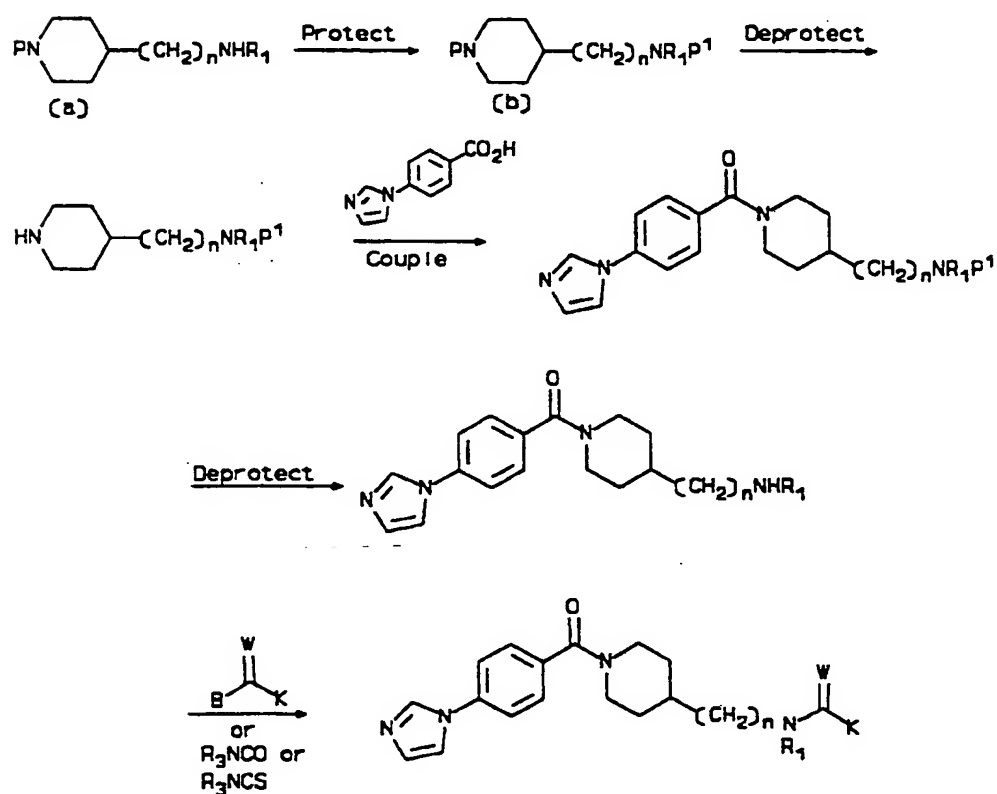
Deprotection of the derivatized compounds (d) makes use of standard methodology appropriate for the protecting group. For example, when P is benzyl or benzyloxycarbonyl, deprotection may be accomplished by catalytic hydrogenolysis employing hydrogen gas at pressures of approximately 50 psi with a palladium catalyst in an alcoholic solvent at temperatures of 20°C to 50°C for 0.5 to 48 hr. When P is *t*-butoxycarbonyl, treatment of (d) with methanolic HCl at 0°C to 20°C for 1 to 5 hr effects deprotection. Standard isolation procedures may be used to obtain the deprotected product (e).

Coupling of the deprotected amines (e) with 4-(1H-imidazol-1-yl)benzoic acid may be accomplished using any standard amide forming method. For example, the benzoic acid may be combined with one equivalent of carbonyldiimidazole in a polar organic solvent such as dimethylformamide at approximately 20° for from 1 to 3 hr. The amine (e) is then added, and the mixture is stirred for 6 to 48 hr. The solvent is

chromatography. In some cases it proves advantageous to isolate the products as their acid addition salts with a pharmaceutically acceptable acid such as methanesulfonic acid.

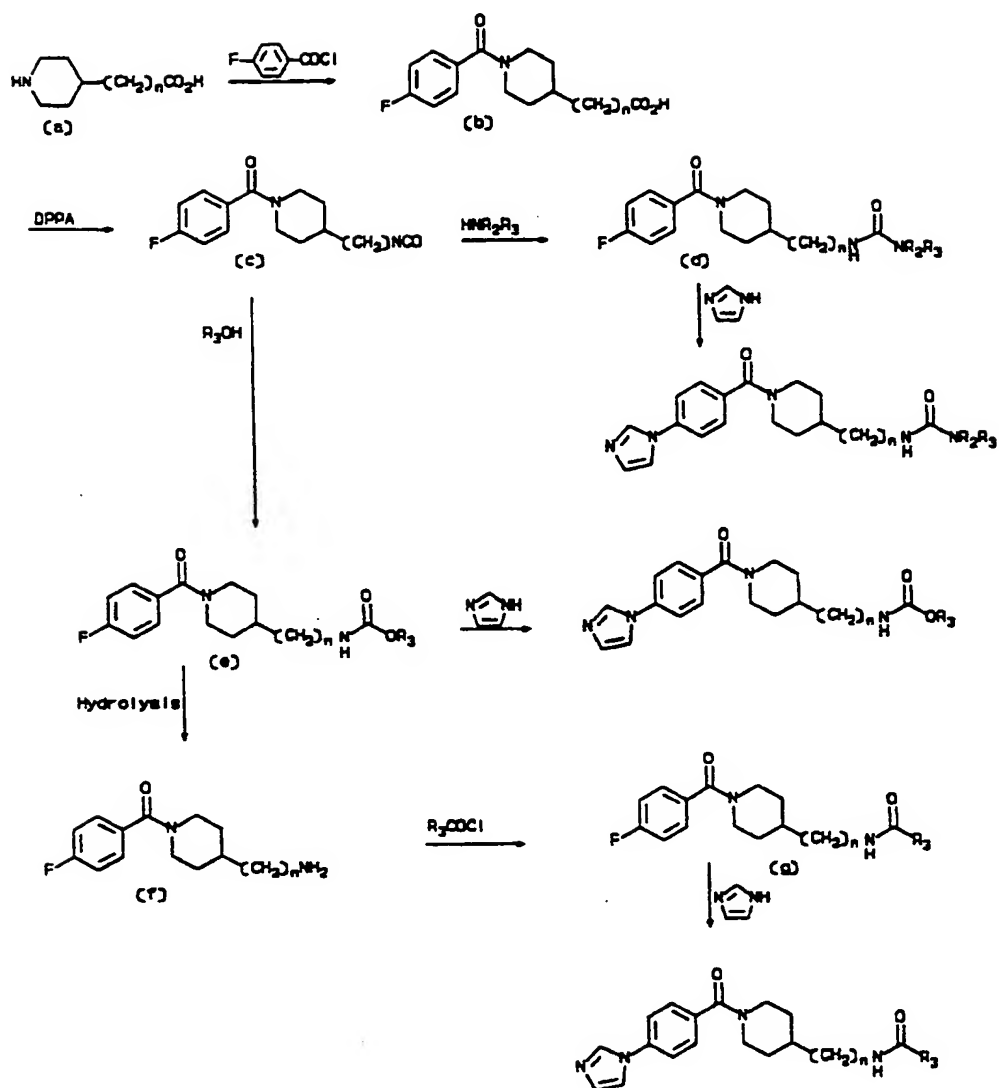
For some compounds of Formula I, it may prove advantageous to use synthetic steps as illustrated in Scheme B.

SCHEME B



An amine (a), prepared as discussed previously, is protected with a protecting group P¹ which can be removed under conditions different from those used to remove P. For example, P can be benzyl and P¹ can be *t*-butoxycarbonyl. In this example, the amine (a) is dissolved in an alcoholic solvent such as methanol and 1.1 equivalents of di-*t*-butyldicarbonate is added. The mixture is stirred for from 15 min to 2 hr at temperatures from 20°C to 70°C, after which the mixture is evaporated, and the crude product is purified by chromatography or crystallization. The process aspects for the remaining operations in Scheme B for the conversion of (b) to compounds of Formula I are generally the same as those described in connection with Scheme A.

Certain compounds of Formula I may be prepared conveniently by an alternative synthesis, shown in Scheme C.

SCHEME C

Piperidine (a) is acylated with 4-fluorobenzoyl chloride. The reactions are generally carried out in a mixture of a water-immiscible organic solvent such as methylene chloride and an aqueous solution of an inorganic base, for example, potassium carbonate. The acid chloride is added dropwise to the solution of the piperidine (a) over 10 min to 1 hr, typically at 0°C to 10°C, after which stirring is continued at 0°C to 25°C for 30 min to 4 hr. The acylated products (b) may be isolated by acidification of the aqueous phase, extraction with an organic solvent, and recrystallization of the residue after evaporation.

Curtius rearrangement of the acids (b) gives the isocyanates (c).

Most conveniently, the acid (b) is combined with one equivalent of diphenylphosphoryl azide (DPPA) and one equivalent of a tertiary amine base, typically triethylamine, in an inert solvent such as toluene. The mixture is heated at 75°C to 100°C under an inert atmosphere for 1 to 3 hr. The resulting solution of the isocyanate (c) is used without isolation. One to two equivalents of a primary or secondary amine may be added to the mixture, and the reaction continued at 20°C to 80°C for 1 to 6 hr to give the ureas (d). Alternatively, an alcohol may be reacted with the isocyanate in a similar fashion to give the carbamates (e). The products (d) and (e) may be isolated by washing the organic mixtures with aqueous acid and aqueous base, followed by evaporation of the organic phase. The crude products may be purified by standard crystallization or chromatographic methods.

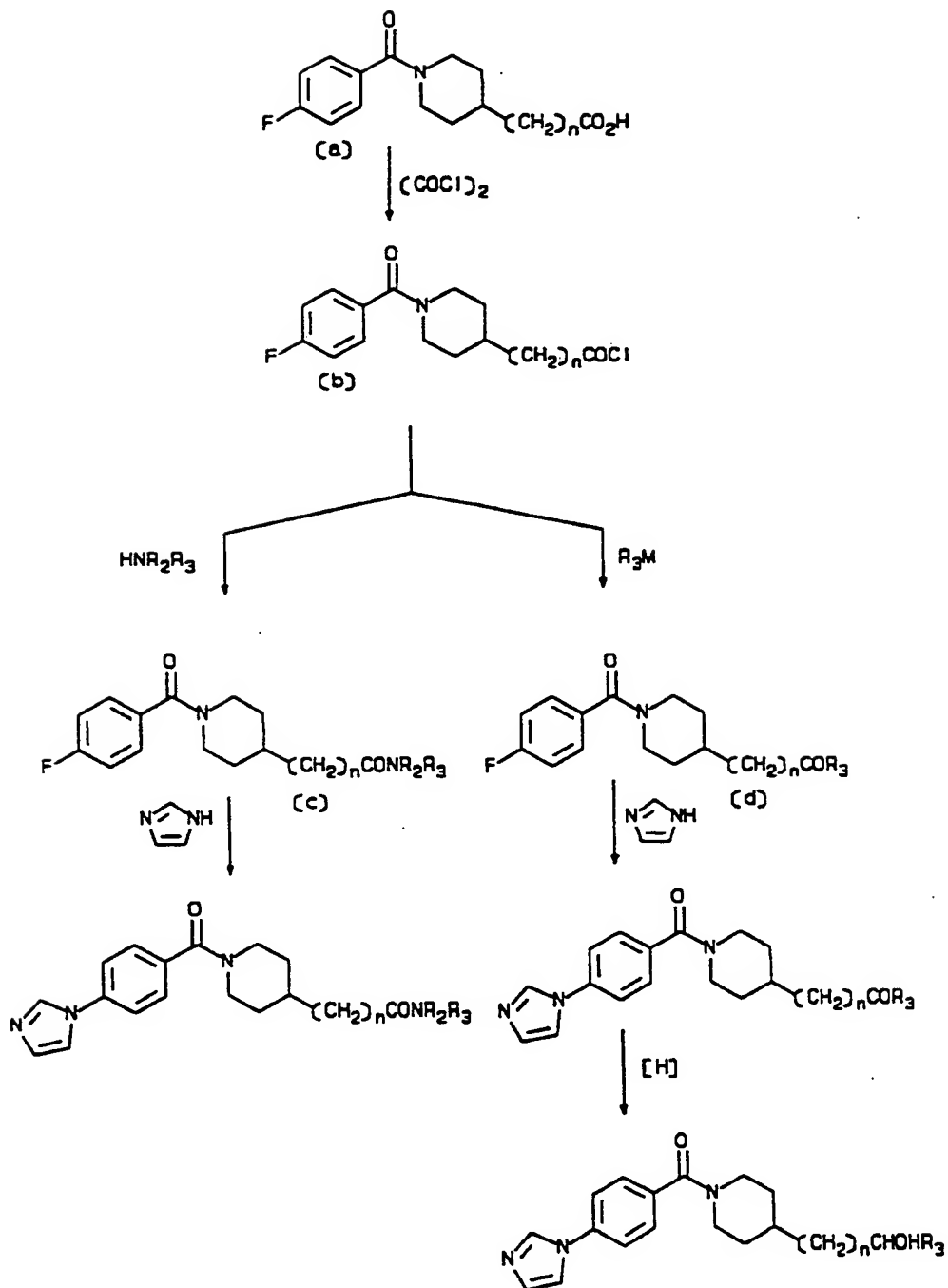
Carbamates (e) may be converted to amines (f) using methodology appropriate to the specific group R_3 . For example, within R_3 is benzyl, the removal may be accomplished by catalytic hydrogenolysis in the presence of hydrogen gas at pressures of about 50 psi with a palladium catalyst in an alcoholic solvent. The reactions are carried out at temperatures of 20°C to 50°C for 0.5 to 48 hr. When R_3 is 2-(trimethylsilyl)ethyl, the carbamate is combined with from 2 to 4 equivalents of cesium fluoride in a polar organic solvent, such as dimethylsulfoxide under an inert atmosphere, and the mixture is heated at 75°C to 100°C for from 2 to 8 hr. The product amines (f) may be isolated by extractive work-up followed by crystallization or chromatographic purification.

Amides (g) are prepared from the amines (f) using standard acylation methods. Typically, the amines are treated with acid chlorides in a mixture of a water-immiscible organic solvent and an aqueous inorganic base, as described previously. The products (g) are isolated by evaporation of the organic phase and recrystallization of the residue.

The fluorine in compounds (d), (e) and (g) may be displaced by imidazole to give the corresponding compounds of Formula I. The fluoro compounds are combined with from 3 to 6 equivalents of imidazole in a polar solvent such as acetonitrile, dimethylformamide, or dimethylsulfoxide, the latter being preferred. In most cases, addition of 1 to 3 equivalents of an

inorganic base such as potassium carbonate is beneficial; however, this is not always necessary. The mixture is heated under an inert atmosphere at from 70°C to 150°C for 12 to 96 hr. The crude product may be isolated by extractive work-up; in some cases, the product may be precipitated by pouring the reaction mixture into water. The product is purified by recrystallization, in some cases as a pharmaceutically acceptable salt.

Compounds of Formula I in which Y is CONR_2R_3 , COR_3 , or CHOHR_3 are prepared as shown in Scheme D.

SCHEME D

Carboxylic acid (a) is converted to its acid chloride (b) using thionyl chloride or oxalyl chloride, preferably the latter. For instance, the acid may be dissolved in an inert solvent such as methylene chloride and treated with 1.0 to 1.2 equivalents of oxalyl chloride at 0°C to 25°C. Trace amounts of dimethylformamide are often useful to catalyze this reaction. The mixture is stirred for from 1 to 4 hr. Evaporation of the solvent provides the crude acid chloride, which may be used without further purification.

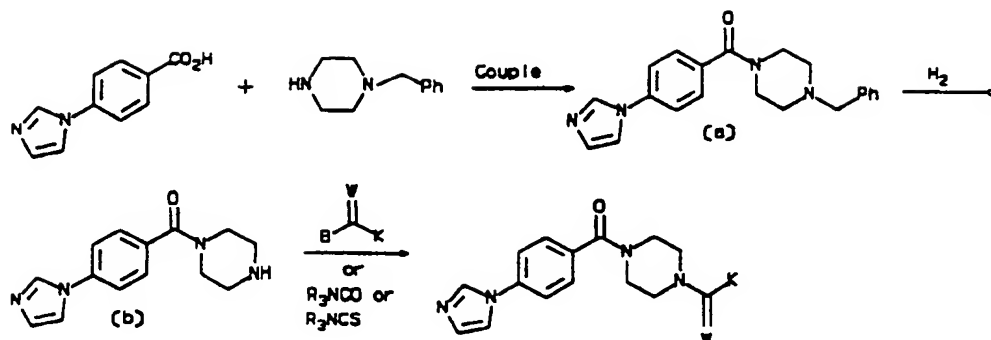
Preparation of amides (c) is accomplished by treatment of the acid chloride (b) with an amine, using standard amide forming reaction conditions, most preferably those involving a two-phase organic solvent and aqueous inorganic base mixture. Compound (c) may then be converted to the corresponding compounds of Formula I by reaction with imidazole, as previously discussed.

Conversion of the acid chloride (b) to ketones (d) is best accomplished by reaction with an organometallic reagent (R_3M), for example, by organocadmium, organocuprate, or copper catalyzed Grignard addition. Most commonly, an organocopper reagent is prepared by reaction of copper (I) iodide with one equivalent of methyllithium in a solvent such as tetrahydrofuran under an inert atmosphere from -80°C to 20°C for 1 hr. The mixture is cooled to -80°C, a Grignard reagent (R_3MgX) is added, and the mixture is stirred from -80°C to 20°C for 1 to 2 hr. The mixture is once more cooled to -80°C, and a solution of the acid chloride (b) is added dropwise

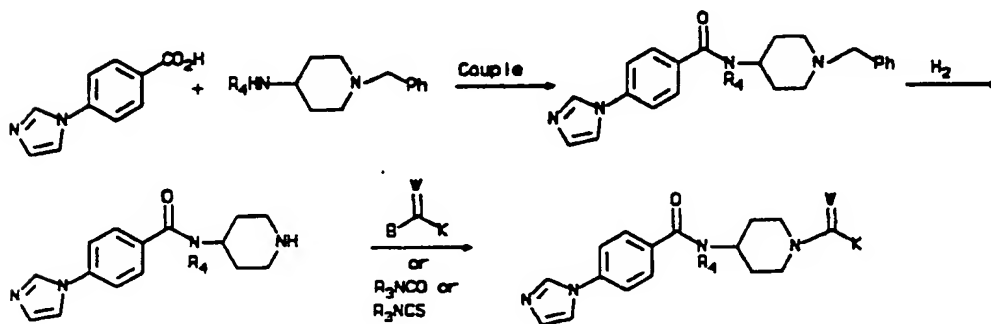
over approximately 30 min. The mixture is then stirred 1 hr at -80°C, 2 to 4 hr at 20°C, and is quenched with aqueous ammonium chloride. Isolation of the product ketone (d) involves partitioning between an organic solvent and aqueous base. At times small amounts of methyl ketone (i.e., R_3 = methyl) may be obtained as impurities in (d). These may be removed by standard chromatographic or crystallization methods.

Compounds (d) may be converted to the corresponding compounds of Formula I by reaction with imidazole, as previously discussed. Keto compounds of Formula I may be reduced by a metal hydride reagent in an appropriate solvent, preferably by sodium borohydride in an alcoholic solvent such as methanol. These reductions are best carried out by treating a solution of the ketone at 0°C to 20°C with 0.5 to 2 equivalents of sodium borohydride for from 30 min to 5 hr. The crude product is obtained by aqueous workup, and purification is effected by crystallization.

Certain compounds of Formula I are most conveniently prepared as shown in Scheme E.

SCHEME E

The process aspects of this preparation are generally similar to those described in connection with Scheme B. Thus, 4-(1H-imidazol-1-yl)benzoic acid is coupled with 1-benzylpiperazine to give amine (a), which is converted to the debenzylated amine (b) by catalytic hydrogenolysis. Derivatization on nitrogen with the appropriate reagents leads to compounds of Formula I. Similarly, other compounds of Formula I may be prepared in an analogous fashion, as shown in Scheme F.

SCHEME F

METHOD-OF-USE AND PHARMACEUTICAL COMPOSITION ASPECTS

The novel imidazolylbenzoyl substituted heterocycles of this invention and their pharmaceutically acceptable salts are antiarrhythmic agents primarily with a Class III antiarrhythmic effect. Certain of the compounds also exhibit a Class I antiarrhythmic effect.

In 1970, Vaughan Williams devised his, by now well known, method for classifying various antiarrhythmic agents. Generally speaking, Class I agents typified for example by flecainide, lidocaine or mexiletine are local anesthetics on nerve and myocardial membranes thereby slowing conduction, which decreases the propagation of ectopic (premature) beats and suppresses the tendency of damaged cells to initiate ectopic beats. The Class II agents are the so-called β -blockers best exemplified by propranolol. The Class III agents represented by bretylium or amiodarone have little or no effect on conduction; in fact, they are quite independent of conduction. They prolong the action potential duration of the heart cells thus increasing the time interval in which the heart cells are unexcitable (refractory period) without slowing conduction or changing the excitability of the cardiac cells.

The compounds of this invention were tested in several biological procedures to analyze their type of antiarrhythmic effect. For instance, utilizing standard electrophysiological techniques, the resting potential, amplitude, duration and rate of rise of phase 0 (depolarization) of the action

potential were measured in normal canine cardiac Purkinje fibers. Those compounds which in this screen demonstrated an increase in action potential duration without a decrease in the rate of rise of phase 0 were designated Class III antiarrhythmic agents. Those compounds which decreased the rate of rise of phase 0 i.e. slowed conduction were designated as Class I agents.

Certain compounds were tested for their vasodilator activity - such compounds would be useful for the treatment of hypertension or heart failure. The compounds were evaluated by assessing vasodilator activity in rings of canine coronary artery and mesenteric vein in vitro.

In general, the compounds of this invention may be administered orally or parenterally. The dosage administered will be dependent on the subject being treated, the route of administration and the type and severity of the arrhythmias being prevented or reduced.

The compound to be administered can be formulated by admixing with any of a number of suitable pharmaceutical diluents and carriers such as lactose, sucrose, starch powder, cellulose, calcium sulfate, sodium benzoate and the like. Such formulations can be compressed into tablets or can be encapsulated into gelatin capsules for convenient oral administration. For parenteral administration a compound of this invention can be formulated as an intramuscular or intravenous medicament but is not limited thereto. In the case of treatment of a patient suffering from severe cardiac

arrhythmias, it may be desirable to administer a compound of this invention by an intravenous slow bolus in order to effect a rapid conversion to a normal sinus rhythm. The normalized condition can then be maintained by oral administration of the compound.

The compounds of this invention can be formulated for parenteral administration with any of a number of pharmaceutically acceptable carriers and diluents to constitute an injectable liquid solution. Commonly used diluents and carriers include water or a saline solution, buffered aqueous solutions as well as dispersing and surface active agents if necessary. Such formulations can be infused at a constant rate or injected one to four times per day or more often depending upon the particular condition of the subject being treated.

It is further contemplated that the compounds of this invention may be formulated into sublingual lozenges or impregnated into fabric appliques for a type of transdermal application.

The pharmaceutical formulations of the compounds of this invention may optionally, additionally contain one or more other pharmaceutically active substances, as for instance combining the compounds of this invention with β -adrenergic blocking agents for the treatment of mammalian subjects who have suffered myocardial infarction.

The invention described hereinabove is illustrated below in the Preparations and Examples, which, however, are not to be construed as limiting the scope of this invention.

PREPARATIONS

Preparation 1

1-(4-Fluorobenzoyl)piperidine-4-carboxylic acid

Piperidine-4-carboxylic acid (25.8 g, 200 mmol) and potassium carbonate (82.9 g, 600 mmol) are combined in water (500 mL) and methylene chloride (1L) at 0°C. 4-Fluorobenzoyl chloride (31.7 g, 200 mmol) is dissolved in methylene chloride (200 mL) and added to the first mixture dropwise over 45 min. The mixture is stirred for 2 hr, after which the aqueous layer is separated and acidified to pH 1.5 with concentrated HCl. The aqueous mixture is extracted three times with methylene chloride, and the organic extracts are dried over magnesium sulfate and evaporated to give the title compound.

NMR (CDCl₃): δ = 1.73(br s,2), 1.97(br s,2), 2.63(m,1), 3.09(br t,2), 3.73(br s,1), 4.48(br s,1), 7.10(t,2), 7.41(m,2).

Preparation 2

In a manner similar to that described in Preparation 1, treat the following reactants, respectively:

- a) 1-(4-Fluorobenzoyl)-4-piperidinamine and hexanoyl chloride,
- b) Piperidine-4-carboxylic acid and benzyl chloroformate, to obtain the following products, respectively:
- c) N-[1-(4-Fluorobenzoyl)-4-piperidiny]hexanamide,
- d) 1-[(Phenylmethoxy)carbonyl]piperidine-4-carboxylic acid.

Preparation 3

N-Butyl-1-(4-fluorobenzoyl)piperidine-4-carboxamide

1-(4-Fluorobenzoyl)piperidine-4-carboxylic acid (8.79 g, 35.0 mmol) is dissolved in methylene chloride (75 mL) at 0°C, and dimethylformamide (0.20 mL) and oxalyl chloride (4.9 g, 39 mmol) are added. The mixture is stirred at room temperature for 2 hr. In a second flask, butylamine (2.6 g, 35 mmol) and potassium carbonate (9.67 g, 75.4 mmol) are dissolved in water (100 mL) and methylene chloride (200 mL) at 0°C. The first mixture is added to the second dropwise over 45 min, and the mixture is stirred at 0°C for 2 hr. The organic phase is separated, washed twice with saturated sodium bicarbonate, twice with 1N HCl, dried over magnesium sulfate, and evaporated. Recrystallization from ethyl acetate-hexane affords the title compound.

NMR (CDCl_3): δ = 0.93(t,3), 1.31(sextuplet,2), 1.49(quint,2), 1.76(m,4), 2.30(m,1), 2.93(m,2), 3.26(quar,2), 3.79(m,1), 4.63(m,1), 5.48(m,1), 7.09(t,2), 7.41(dd,2).

Preparation 4

1-(4-Fluorobenzoyl)-4-(2-oxohexyl)piperidine

1-(4-Fluorobenzoyl)piperidine-4-carboxylic acid (11.31 g, 45.0 mmol) is dissolved in methylene chloride (100 mL) at 0°C, and dimethylformamide (0.20 mL) and oxalyl chloride (5.8 g, 46 mmol) are added. The mixture is stirred 3 hr at room temperature, after which the solvent is evaporated; toluene (50 mL) is added and evaporated under reduced pressure. The toluene treatment is then repeated. In a second flask, copper (I) iodide (8.57 g, 45.0 mmol) is suspended in tetrahydrofuran (100 mL) at -78°C under a nitrogen atmosphere. Methylolithium (1.55 M in ether, 29 mL, 45 mmol) is added, and the mixture is stirred at room temperature for 50 min. The mixture is cooled to -78°C, and pentylmagnesium bromide (2.0 M in ether, 22.5 mL, 45 mmol) is added. The mixture is stirred for 15 min at -78°C, 1.5 hr at room temperature, and is cooled to -78°C. A solution of the first residue in tetrahydrofuran (30 mL) is added to the second mixture dropwise over 30 min, and the mixture is stirred 1 hr at -78°C, and then 3 hr at room temperature. The mixture is poured into saturated ammonium chloride (500 mL), sodium hydroxide (1 g) is added, and the mixture is stirred 16 hr. The layers are separated, the aqueous phase is extracted twice with methylene chloride, and the combined organics are washed twice

with 1N sodium hydroxide, once with brine, dried over magnesium sulfate, and evaporated. The residue is chromatographed on silica gel eluting with hexane and ethyl acetate mixtures and recrystallized from ether-petroleum ether to afford the title compound.

NMR (CDCl_3): δ = 0.89(t,3), 1.28(m,4), 1.58(m,4), 1.85(br s,2), 2.47(t,2), 2.60(m,1), 2.99(br s,2), 3.79(br s,1), 4.57(br s,1), 7.09(t,2), 7.40(dd,2).

Preparation 5

1-(4-Fluorobenzoyl)-4-(1-oxoethyl)piperidine

In a manner similar to that described in Preparation 4, 1-(4-fluorobenzoyl)piperidine-4-carboxylic acid is reacted with methylmagnesium bromide to afford the title compound.

NMR (CDCl_3): δ = 1.64(m,2), 1.88(m,2), 2.20(s,3), 2.62(m,1), 3.01(br s,2), 3.73(br s,1), 4.54(br s,1), 7.11(t,2), 7.41(m,2).

Preparation 6

1-(4-Fluorobenzoyl)-4-piperidinylcarbamic acid,

2-(trimethylsilyl)ethyl ester

1-(4-Fluorobenzoyl)piperidine-4-carboxylic acid (10.05 g, 40.0 mmol) and triethylamine (4.1 g, 40 mmol) are combined in toluene (50 mL) under a nitrogen atmosphere. Diphenylphosphoryl azide (11.0 g, 40.0 mmol) is added, and the mixture is heated at 80°C for 2 hr. 2-(Trimethylsilyl)ethanol (9.49 g, 80.2 mmol) is added, and the mixture is stirred at 80°C for 2 hr, and

room temperature for 2 hr. The mixture is diluted with methylene chloride, washed twice with 1N HCl, twice with 0.5 N sodium hydroxide, dried over magnesium sulfate, and evaporated. The residue is recrystallized from ether-hexane to afford the title compound.

NMR (CDCl_3): δ = 0.04(s,9), 0.98(m,2), 1.31(m,2), 1.91(m,2), 2.99(m,2), 3.67(m,2), 4.15(m,2), 4.59(m,2), 7.11(t,2), 7.42(dd,2).

Preparation 7

4-[[[(Butoxy)carbonyl]amino]piperidine-1-carboxylic acid, phenylmethyl ester

In a manner similar to that described in Preparation 6, 1-[(phenylmethoxy)carbonyl]piperidine-4-carboxylic acid and 1-butanol are reacted to give the title compound.

Preparation 8

1-(4-Fluorobenzoyl)-4-piperidinamine hydrochloride

[[1-(4-Fluorobenzoyl)-4-piperidinyl]]carbamic acid 2-(trimethylsilyl)ethyl ester (14.66 g, 40.0 mmol) and cesium fluoride (12.14 g, 79.9 mmol) are combined in dimethyl sulfoxide (100 mL) under a nitrogen atmosphere and heated to 80°C for 4 hr. The mixture is poured onto water (1 L) and extracted three times with methylene chloride. The organic extracts are dried over magnesium sulfate and evaporated to provide the title compound as its free base. The material is converted to its hydrochloride salt and recrystallized from 2-propanol-ether to provide the title compound.

NMR (DMSO- d_6): δ = 1.49(m,2), 1.94(br s,2), 2.84-3.19(m,2), 3.33(m,1), 3.61(br s,1), 4.42(br s,1), 7.30(t,2), 7.60(dd,2), 8.27(br,3).

Preparation 9

N-Methyl-1-(phenylmethyl)-4-piperidinamine dihydrochloride

1-(Phenylmethyl)-4-piperidone (18.99 g, 100 mmol), methylamine hydrochloride (6.75 g, 100 mmol), and 3 Å molecular sieves (54 g) are combined in methanol (350 mL), and the mixture is stirred 2 hr. Acetic acid (2 mL) and sodium cyanoborohydride (4.19 g, 66.7 mmol) are added, and the mixture is stirred for 48 hr at room temperature. The mixture is filtered through Celite, diluted with 1 N sodium hydroxide, and extracted three times with methylene chloride. The organic extracts are dried over magnesium sulfate and evaporated to give the title compounds as its free base. The material is converted to its hydrochloride salt and recrystallized from methanol-ether to give the title compound.

NMR (DMSO- d_6) : δ = 2.05(m,2), 2.25(m,2), 3.00(m,2), 3.18(m,1), 3.40(m,5), 4.29(br s,2), 7.48(m,3), 7.63(m,2), 9.47(br s,2), 11.18(br s,1).

Preparation 10

N-Butyl-N'-[1-(phenylmethyl)-4-piperidinyl]urea

Butyl isocyanate (33.9 g, 342 mmol) is added dropwise to a solution of 1-(phenylmethyl)-4-piperidinamine (65 g, 342 mmol) in methylene chloride (400 mL) at 0°C, and the mixture is stirred for 2 hr. The mixture is washed three times with water, dried over magnesium sulfate, and evaporated.

Recrystallization of the residue from methylene chloride-hexane affords the title compound.

NMR (CDCl₃) : δ = 0.91(t,3), 1.3-1.6(m,6), 1.91(m,2), 2.1(dt,2), 2.8(d,2), 3.13(quar,2), 3.48(s,2), 3.60(m,1), 4.35(d,1), 4.45(t,1), 7.20-7.50(m,5).

Preparation 11

N-Butyl-N'-methyl-N'-[1-(phenylmethyl)-4-piperidinyl]urea hydrochloride

In a manner similar to that described in Preparation 10, butyl isocyanate is reacted with N-methyl-1-(phenylmethyl)-4-piperidinamine to afford the title compound.

NMR (DMSO-d₆) : δ = 0.88(t,3), 1.26(sextet,2), 1.39(quin,2), 1.62(br d,2), 2.12(br quar,2), 2.64(s,3), 3.02(m,4), 3.31(m,2), 4.28(m,3), 6.32(t,1), 7.48(m,3), 7.65(m,2), 10.96(br s,1).

Preparation 12

[1-(Phenylmethyl)-4-piperidinyl]carbamic acid, 1,1-dimethylethyl ester

1-(Phenylmethyl)-4-piperidinamine (78 g, 410 mmol) is dissolved in methanol (400 mL) and di-tert-butyl dicarbonate (95 g, 440 mmol) is added over 5 min. The solution is stirred 15 min at room temperature, 20 min at 70°C, and then evaporated. Trituration of the residue with ether affords the title compound.

NMR (CDCl_3) : δ = 1.44(m,11), 1.88(m,2), 2.08(t,2), 2.78(m,2), 3.48(m,3), 4.42(br s,1), 7.31(m,5).

Preparation 13

1-[4-(1H-imidazol-1-yl)benzoyl]-4-(phenylmethyl)piperazine methanesulfonic acid salt (1:2)

4-(1H-imidazol-1-yl)benzoic acid (18.82 g, 100 mmol) and carbonyl-diimidazole (16.22 g, 100 mmol) are combined in dimethylformamide (200 mL) and stirred for 2 hr. 1-(Phenylmethyl)piperazine (17.7 g, 101 mmol) is added, and the mixture is stirred for 20 hr. The solvent is evaporated, and the residue is dissolved in methylene chloride and washed twice with saturated aqueous sodium bicarbonate, twice with water, and dried over magnesium sulfate. Evaporation of the solvent and recrystallization of the residue from ethyl acetate-hexane provides the free base of the title compound. Conversion to the methanesulfonic acid salt and recrystallization from ethanol-ether affords the title compound.

NMR ($\text{DMSO}-d_6$): δ = 2.37(s,6), 3.01-3.88(br m,8), 4.39(s,2), 7.50(m,3), 7.55(m,2), 7.74(d,2), 7.95(m,3), 8.35(s,1), 9.73(s,1).

Preparation 14

In a manner similar to that described in Preparation 13, 4-(1H-imidazol-1-yl)benzoic acid is reacted with the following reactants, respectively:

- a) (4-Piperidiny)carbamic acid, 1,1-dimethylethyl ester,

- b) 1-(Phenylmethyl)-4-piperidinamine, to provide the following products, respectively:
- c) [1-[4-(1H-Imidazol-1-yl)benzoyl]-4-piperidiny]carbamic acid, 1,1-dimethylethyl ester,
- d) 4-(1H-Imidazol-1-yl)-N-[1-(phenylmethyl)-4-piperidiny]-benzamide.

Preparation 15

1-[4-(1H-Imidazol-1-yl)benzoyl]piperazine

1-[4-(1H-Imidazol-1-yl)benzoyl]-4-(phenylmethyl)piperazine (26.65 g, 76.9 mmol) is dissolved in ethanol (500 mL) and 10% palladium on carbon (2.00 g) as a slurry in water (10 mL) is added to the solution. The mixture is shaken under an atmosphere of hydrogen on a Parr apparatus at 50 psi and 50°C for 30 hr. The mixture is filtered through Celite, the solvent is evaporated, and the residue is triturated with ether and crystallized from ethyl acetate-hexane to afford the title compound.

NMR (CDCl₃): δ = 1.76(br s,1), 2.90(br m,4), 3.43(br s,2), 3.76(br s,2), 7.23(s,1), 7.31(s,1), 7.45(d,2), 7.55(d,2), 7.89(s,1).

Preparation 16

In a manner similar to that described in Preparation 15, the following reactants, respectively:

- a) [1-(Phenylmethyl)-4-piperidiny]carbamic acid, 1,1-dimethylethyl ester,

- b) 4-(1H-Imidazol-1-yl)-N-[1-(phenylmethyl)-4-piperidiny]-benzamide,
- c) N-Butyl-N'-methyl-N'-[1-(phenylmethyl)-4-piperidiny]urea hydrochloride,
- d) N-Butyl-N'-[1-(phenylmethyl)-4-piperidiny]urea,
- e) 4-[[[(Butoxy)carbonyl]amino]piperidine-1-carboxylic acid, phenylmethyl ester.

are converted to the following products, respectively:

- f) (4-Piperidiny)carbamic acid, 1,1-dimethylethyl ester,
- g) 4-(1H-Imidazol-1-yl)-N-(4-piperidiny)benzamide,
- h) N-Butyl-N'-methyl-N'-(4-piperidiny)urea hydrochloride,
- i) N-Butyl-N'-(4-piperidiny)urea,
- j) (4-Piperidiny)carbamic acid, butyl ester.

Preparation 17

1-[4-(1H-Imidazol-1-yl)benzoyl]-4-piperidinamine dihydrochloride

[1-(4-(1H-Imidazol-1-yl)benzoyl)-4-piperidiny]carbamic acid, 1,1-dimethylethyl ester (131.6 g, 355 mmol) is dissolved in methanol (800 mL) at 0°C, and the solution is saturated with HCl gas. The mixture is stirred for 3 hr at room temperature, after which ether is added to give a turbid solution. The resulting precipitate is collected and air dried to afford the title compound.

NMR (DMSO- d_6): δ 1.63(m,2), 1.97(m,1), 2.06(m,1), 2.96(m,1),
3.21(m,1), 3.33(m,2), 3.60(m,1), 4.50(m,1), 7.65(d,2), 7.96(s,1), 7.97(d,2),
8.39(s,1), 8.57(br s,3), 9.85(s,1).

EXAMPLES

Example 1

N-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidiny]hexanamide

N-[1-(4-Fluorobenzoyl)-4-piperidiny]hexanamide (5.73 g, 17.9 mmol)
imidazole (6.09 g, 89.5 mmol), and potassium carbonate (4.59 g, 35.8 mmol)
are combined in dimethylsulfoxide (75 mL) under a nitrogen atmosphere,
and the mixture is heated at 130°C for 42 hr. The mixture is cooled, poured
on water, and extracted with methylene chloride. The extracts are washed
with brine, dried over magnesium sulfate, and evaporated. Recrystallization
of the residue from ethyl acetate provides the title compound.

NMR (CDCl₃): δ = 0.89(t,3), 1.31(m,6), 1.61(quin,2), 2.00(m,2),
2.16(t,2), 2.96(m,1), 3.13(m,1), 3.73(m,1), 4.03(m,1), 4.63(m,1), 5.45(d,1),
7.24(s,1), 7.31(s,1), 7.45(d,2), 7.54(d,2), 7.90(s,1).

Example 2

In a manner similar to that described in Example 1, the following
reactants, respectively:

- a) N-Butyl-1-(4-fluorobenzoyl)piperidine-4-carboxamide,
- b) 1-(4-Fluorobenzoyl)-4-(1-oxohexyl)piperidine,

c) 1-(4-Fluorobenzoyl)-4-(1-oxoethyl)piperidine,

are converted to the following products, respectively:

d) N-Butyl-1-[4-(1H-imidazol-1-yl)benzoyl]piperidine-4-

carboxamide, methanesulfonic acid salt,

e) 1-[4-(1H-imidazol-1-yl)benzoyl]-4-(1-oxohexyl)piperidine,

f) 1-[4-(1H-imidazol-1-yl)benzoyl]-4-(1-oxoethyl)piperidine

hydrochloride.

Example 3

4-(1-Hydroxyhexyl)-1-[4-(1H-imidazol-1-yl)benzoyl]piperidine,

methanesulfonic acid salt

1-[4-(1H-imidazol-1-yl)benzoyl]-4-(1-oxohexyl)piperidine (0.67 g, 1.90 mmol) is dissolved in methanol (10 mL) at 0°C, and sodium borohydride (72 mg, 1.9 mmol) is added. The mixture is stirred for 3 hr at 0°C, after which it is diluted with water and made acidic with 2 N HCl. The solution is washed three times with methylene chloride, made basic with sodium carbonate, and extracted with methylene chloride. The extracts are dried with magnesium sulfate and evaporated to a residue. Recrystallization of the product as its methanesulfonic acid salt from ethanol-ether provides the title compound.

NMR (DMSO- d_6): δ = 0.87(t,3), 1.10-1.88(m,13), 2.24(s,3), 2.72(br s,1), 3.01(br s,1), 3.21(br s,1), 3.52(br m,1), 4.54(br m,1), 7.64(d,2), 7.89(d,2), 7.94(s,1), 8.34(s,1), 9.71(s,1).

Exempl 4**N-Butyl-N'-[1-[4-(1H-imidazol-1-yl)benz yl]-4-piperidinyl]-****N'-methylurea methanesulfonic acid salt**

4-(1H-imidazol-1-yl)benzoic acid (4.52 g, 24.0 mmol) and carbonyl-diimidazole (3.89 g, 24.0 mmol) are combined in dimethylformamide (50 mL) and the mixture is stirred 2 hr. A solution of N-butyl-N'-methyl-N'-(4-piperidinyl)urea (6.00 g, 24.0 mmol) in dimethylformamide (25 mL) is added, and the mixture is stirred 18 hr. The solvent is removed by evaporation and the residue is dissolved in methylene chloride. The solution is washed twice with saturated aqueous sodium bicarbonate and twice with water, dried over magnesium sulfate, and evaporated to a residue. Recrystallization of the crude product as its methanesulfonic acid salt from ethanol-ether provides the title compound.

NMR (DMSO- d_6) : δ = 0.87(t,3), 1.25(sextet,2), 1.37(quin,2), 1.61(br s,4), 2.35(s,3), 2.66(s,3), 2.84(br m,1), 3.01(m,2), 3.13(br m,1), 3.55(br m,1), 4.21(br m,1), 4.57(br m,1), 6.27(br s,1), 7.70(d,2), 7.90(d,2), 7.95(s,1), 8.35(s,1), 9.73(s,1).

Example 5**N-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidinyl]-3-pyridinecarboxamide**

In a manner similar to that described in Example 4, nicotinic acid and 1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidinamine are converted to the title compound.

Exempl 6**N-Butyl-N'-[1-[4-(1H-imidazol-1-yl)benz yl]-4-piperidinyl]urea****methanesulfonic acid salt**

4-(1H-imidazol-1-yl)benzoic acid (2.6 g, 13.9 mmol), toluene (35 mL), and thionyl chloride (35 mL) are combined and heated at 70°C for 1.5 hr, after which the mixture is evaporated. The residue is combined with N-butyl-N'-(4-piperidinyl)urea (2.0 g, 10 mmol) in methylene chloride (40 mL) at -78°C under a nitrogen atmosphere, and triethylamine (4 mL) in methylene chloride (10 mL) is added dropwise. The mixture is allowed to warm to room temperature and is stirred for three days. The mixture is evaporated to a residue which is triturated with ethanol. The ethanol is evaporated, and the residue is chromatographed on silica. The chromatographed material is converted to its methanesulfonic acid salt and recrystallized from isopropanol-acetonitrile to yield the title compound.

NMR (DMSO- d_6): δ = 0.84(t,3), 1.30(m,6), 1.74-1.84(br,1), 2.32(s,3), 2.96(t,3), 3.00-3.90(br,13), 4.28(br,1), 5.80-5.84(br,2), 7.68(d,2), 7.90(d,2), 7.93(s,1), 8.34(s,1), 9.68(s,1).

Example 7**[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidinyl]carbamic acid****butyl ester, methanesulfonic acid salt**

In a manner similar to that described in Example 6, 4-(1H-imidazol-1-yl)benzoic acid and (4-piperidinyl)carbamic acid, butyl ester are reacted to give the title compound.

Exempl 8**N-Butyl-N'-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidinyl]thi urea**

1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidinamine (4.06 g, 15.0 mmol) and butyl isothiocyanate (1.81 mL, 1.73 g, 15.0 mmol) are combined in methylene chloride (75 mL) and stirred at room temperature. After 24 hr, an additional portion (0.90 mL, 0.86 g, 7.5 mmol) of butyl isothiocyanate is added, and the mixture is stirred for 48 hr. The mixture is washed twice with 1N aqueous sodium hydroxide, once with brine, dried over magnesium sulfate, and evaporated. Trituration of the residue with ether and recrystallization from ethanol-ether affords the title compound.

NMR (DMSO- d_6): δ = 0.89(t,3), 1.31(m,2), 1.46(m,4), 1.91(br s,2), 3.00(br s,1), 3.13(br s,1), 3.40(br s,2), 3.60(br s,1), 4.33(br s,2), 7.15(s,1), 7.32(br m,2), 7.54(d,2), 7.76(d,2), 7.83(s,1), 8.36(s,1).

Example 9

In a manner similar to that described in Example 8, the following reactants, respectively:

- a) 1-[4-(1H-imidazol-1-yl)benzoyl]piperazine,
- b) N-(4-Piperidinyl)-4-(1H-imidazol-1-yl)benzamide,

are reacted with butyl isocyanate to give the following products, respectively:

- c) N-Butyl-4-[4-(1H-imidazol-1-yl)benzoyl]piperazine-1-carboxamide,
- d) N-Butyl-4-[[4-(1H-imidazol-1-yl)benzoyl]amino]piperidine-1-carboxamide.

Example 10**N-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidinyl]benzenepropanamide**

1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidinamine dihydrochloride (4.46 g, 13.0 mmol) and potassium carbonate (6.67 g, 52.0 mmol) are dissolved in methylene chloride (60 mL) and water (30 mL) and the mixture is cooled with an ice bath. A solution of 3-phenylpropionyl chloride (2.72 g, 16.2 mmol) in methylene chloride (15 mL) is added dropwise over 15 min, and the mixture is stirred at room temperature for 2 hr. The phases are separated, and the organic phase is washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and evaporated. Chromatography of the residue on silica gel followed by recrystallization from acetonitrile affords the title compound.

NMR (DMSO- d_6): δ = 1.30(br s,2), 1.74(br s,2), 2.37(t,2), 2.82(t,2), 3.10(br s,2), 3.55(br s,1), 3.82(br m,1), 4.27(br s,1), 7.14(s,1), 7.17-7.29(m,5), 7.51(d,2), 7.75(d,2), 7.83(m,2), 8.34(s,1).

Example 11**N-[1-[4-(1H-imidazol-1-yl)-benzoyl]-4-piperidinyl]-2,6-dimethylbenzamide**

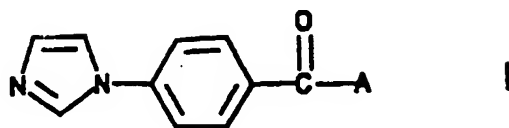
In a manner similar to that described in Example 10, 1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidinamine dihydrochloride and 2,6-dimethylbenzoyl chloride are reacted to give the title compound.

CLAIMS

We claim

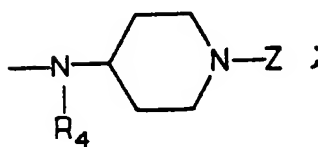
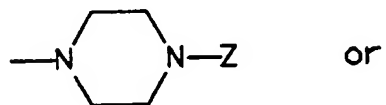
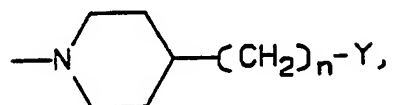
-1-

A compound of the following Formula I:

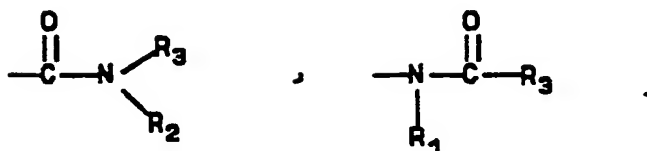
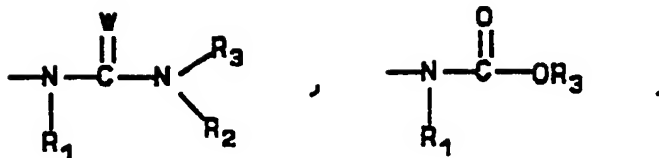


wherein

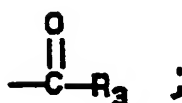
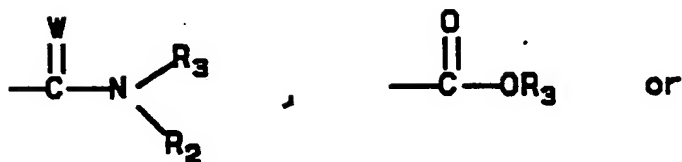
A is



Y is



Z is

W is O, S, NR, NCN or CHNO₂;

R is selected from hydrogen, C₁-C₄ straight or branched chain alkyl,
optionally substituted aryl or arylalkyl;

R_1 , R_2 , R_4 are independently hydrogen or C_1 - C_4 straight or branched chain alkyl;

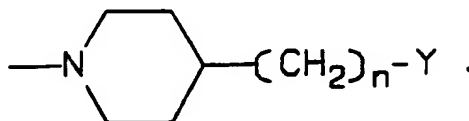
R_3 is selected from C_1 - C_8 straight or branched alkyl, optionally substituted aryl or arylalkyl or heteroaryl;

n is the integers 0, 1 or 2,
and the pharmaceutically acceptable salts thereof;

with the provisos that when R_3 is a C_1 - C_8 straight or branched chain alkyl this is not inclusive of a tertiary moiety and when R_3 is heteroaryl, said heteroaryl cannot be attached to a hetero atom e.g. N or O.

-2-

A compound of claim 1 wherein A is



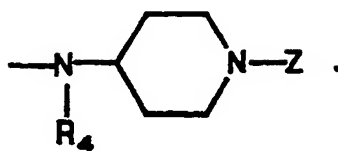
-3-

A compound of claim 1 wherein A is



-4-

A compound of claim 1 wherein A is



-5-

A compound of claim 2 which is N-butyl-N'-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidiny]urea.

-6-

A compound of claim 2 which is N-butyl-N'-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidiny]-N'-methylurea.

-7-

A compound of claim 2 which is N-butyl-N'-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidiny]thiourea.

-8-

A compound of claim 2 which is 4-[[[(3,5-dichlorophenyl)amino]-carbonyl]amino-1-[4-(1H-imidazol-1-yl)benzoyl]piperidine.

-9-

A compound of claim 2 which is N-[[[(3,5-dichlorophenyl)amino]-(imino)methyl]-1-[4-(1H-imidazol-1-yl)benzoyl]piperidine-4-amine.

-10-

A compound of claim 2 which is [1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidinyl]carbamic acid, butyl ester.

-11-

A compound of claim 2 which is N-butyl-1-[4-(1H-imidazol-1-yl)benzoyl]piperidine-4-carboxamide.

-12-

A compound of claim 2 which is N-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidinyl]hexanamide.

-13-

A compound of claim 2 which is N-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidinyl]benzenepropanamide.

-14-

A compound of claim 2 which is N-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidinyl]-2,6-dimethylbenzamide.

-15-

A compound of claim 2 which is N-[1-[4-(1H-imidazol-1-yl)benzoyl]-4-piperidiny]-3-pyridinecarboxamide.

-16-

A compound of claim 2 which is 1-[4-(1H-imidazol-1-yl)benzoyl]-4-(1-oxohexyl)piperidine.

-17-

A compound of claim 2 which is 1-[4-(1H-imidazol-1-yl)benzoyl]-4-(1-oxoethyl)piperidine.

-18-

A compound of claim 2 which is 4-(1-hydroxyhexyl)-1-[4-(1H-imidazol-1-yl)benzoyl]piperidine.

-19-

A compound of claim 3 which is N-butyl-4-[4-(1H-imidazol-1-yl)-benzoyl]piperazine-1-carboxamide.

-20-

A compound of claim 4 which is N-butyl-4-[[4-(1H-imidazol-1-yl)-benzoyl]amino]piperidine-1-carboxamide.

-21-

The method of treating arrhythmias in a mammalian subject in need thereof comprising, administering to said subject an antiarrhythmically effective dose of a compound according to Claim 1.

-22-

A pharmaceutical composition comprising a therapeutically effective amount of at least one compound according to claim 1, together with one or more non-toxic pharmaceutically acceptable carriers.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 91/01137

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl.5	C 07 D 401/10	C 07 D 401/12
A 61 K 31/445	A 61 K 31/495	C 07 D 403/10
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl.5	C 07 D 233/00 A 61 K 31/00	C 07 D 401/00 C 07 D 403/00
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	US,A,4868194 (A.A. CARR et al.) 19 September 1989, see claims ----	1,22
Y	EP,A,0290377 (SCHERING AG.) 9 November 1988, see claims ----	1,22
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 33, no. 4, April 1990, T.K. MORGAN Jr. et al.: "Synthesis and cardiac electrophysiological activity of N-substituted-4-(1H-imidazol-1-yl)benzamides-new selective class III agents", pages 1091-1097, see the whole article, especially page 1092, table I -----	1,22
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
29-08-1991	03. 10. 91	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	Falk Heck	

WEITERE ANGABEN ZU BLATT 2

V. ☒ **BEMERKUNGEN ZU DEN ANSPRÜCHEN, DIE SICH ALS NICHT RECHERCHIERBAR ERWIESEN HABEN** ¹

Gemäß Artikel 17 Absatz 2 Buchstabe a sind bestimmte Ansprüche aus folgende Gründen nicht Gegenstand der internationalen Recherche gewesen:

1. ☒ Ansprüche Nr. 21 weil sie sich auf Gegenstände beziehen, die zu recherchieren die Behörde nicht verpflichtet ist, nämlich:
siehe PCT Regel 39.1(iv)

2. ☐ Ansprüche Nr. weil sie sich auf Teile der internationalen Anmeldung beziehen, die den vorgeschriebenen Anforderungen so wenig entsprechen, daß eine sinnvolle internationale Recherche nicht durchgeführt werden kann, nämlich:

3. ☐ Ansprüche Nr. weil sie abhängige Ansprüche und nicht entsprechend Satz 2 und 3 der Regel 6.4(a) PCT abgefaßt sind.

VI. ☐ **BEMERKUNGEN BEI MANGELNDER EINHEITLICHKEIT DER ERFINDUNG** ²

Die Internationale Recherchenbehörde hat festgestellt, daß diese internationale Anmeldung mehrere Erfindungen enthält:

1. ☐ Da der Anmelder alle erforderlichen zusätzlichen Recherchegebühren rechtzeitig entrichtet hat, erstreckt sich der Internationale Recherchenbericht auf alle recherchierbaren Ansprüche der internationalen Anmeldung.
2. ☐ Da der Anmelder nur einige der erforderlichen zusätzlichen Recherchegebühren rechtzeitig entrichtet hat, erstreckt sich der Internationale Recherchenbericht nur auf die Ansprüche der internationalen Anmeldung, für die Gebühren gezahlt worden sind, nämlich
3. ☐ Der Anmelder hat die erforderlichen zusätzlichen Recherchegebühren nicht rechtzeitig entrichtet. Der Internationale Recherchenbericht beschränkt sich daher auf die in den Ansprüchen zuerst erwähnte Erfindung; sie ist in folgenden Ansprüchen erteilt:
4. ☐ Da für alle recherchierbaren Ansprüche eine Recherche ohne einen Arbeitsaufwand durchgeführt werden konnte, der eine zusätzliche Recherchegebühr gerechtfertigt hätte, hat die Internationale Recherchenbehörde eine solche Gebühr nicht verlangt.

Bemerkung hinsichtlich eines Widerspruchs

- ☐ Die zusätzlichen Gebühren wurden vom Anmelder unter Widerspruch gezahlt.
- ☐ Die Zahlung zusätzlicher Gebühren erfolgte ohne Widerspruch

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

EP 9101137

SA 48350

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 19/09/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4868194	19-09-89	AU-A- 4152689	29-03-90
		EP-A- 0360275	28-03-90
		JP-A- 2124885	14-05-90
EP-A- 0290377	09-11-88	US-A- 4804662	14-02-89